Oxidation Products of Sulfanilamide

By Takuo Kosuge and Tadakazu Tsuzi

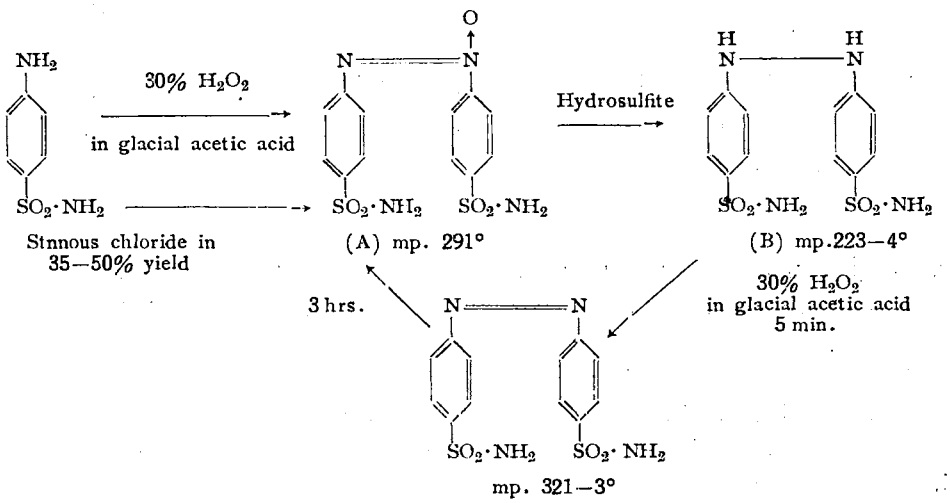
Oxidations of sulfanilamide were caried out to search the more active antibacterial compounds than sulfanilamide.

Although the expected active antibacterial compounds were not discovered from the oxidation products, some interesting behaviors of the oxidation products and the related compounds were observed during the course of the experiments.

Oxidation of the sulfanilamide with hydrogenperoxide was not effected at the low temperature, however when sulfanilamide was treated with concentrated hydrogen peroxide on the water bath (without another solvent), the oxidation occured smoothly. The reaction was complete after 4 to 6 hours. And fine red crystals were obtained,

Margaret K. Seikel[1] had also obtained the fine red crystals by oxidizing sulfanilamide in glacial acetic acid solution by hydrogen peroxide. She concluded that the red crystals were azoxy-compounds(A) and product(B), obtained reducing(A) by hydrosulfite was hydrazo-compound from their analytical values and some chemical properties.

Results obtained by her summarized in the following table.



Her conclusion is very suitable, because it was deduced from exactory precise analytical values. But about this conclusion, there are some apprehensions, because of the following facts.

1) Azoxy-compound was reduced to hydrazo compound with hydrosulfite which reduced in the usual case the azoxy-compoumd to the amine. (The present authors found that very small amount of sulfanilamide was formed).

2) Reduction of (A) with stannous chloride produced no more than 50% yield of sulfanilamide. (The present au-

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thors obtained sulfanilamide in 15 to 20% yield by reduction with tin and hydrochloric acid.)

3) Reduction product of (A) by hydrosulfite, developed color towards "Fichten-holzspan" test as both carbazole and pyrrol do.

4) And the product, dissolved in concentrated sulfuric acid developed red color towards aldehydes as carbazole and pyrrol do.

Then it was our main concern that Margaret K. Seikels conclusion is correct or not.

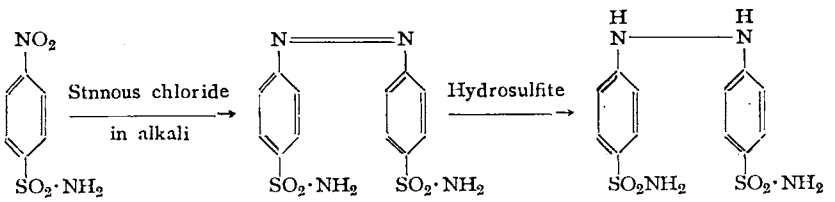
Azoxy-compound was prepared in almost quantitative yield by reduction of p-nitrobenzene-sulfonamide with stannous chloride in alkali media, but hydrazo-compound was not obtained by the same procedure, although stannous chloride was used in more quantity, and that will be due to the fact that hydrazo-compound is unstable when warmed in alkali media.

The azoxy-compound was reduced hydrazo-compound with hydrosulfite.

The azo-compound and hydroazo-compound were identical to the compounds respectively, obtained from the oxidation products, in melting point, analytical value and absorption spectrum.

Materials (A and B) from the oxidation products did not lower the melting point of these compounds (C and D).

But of course this can be not decicive evidence, because this is not melting point but decomposition point.



(C) (D)

From the facts mentioned above, Margaret K. Seikel's conclusion was exactory suitable.

It is intersting that reduction of azo-compound with hydrosulfite was blocked at the state of hydraso-compound, although hydrosulfite is very strong reducing agent. Even when much amount of hydrosulfite were employed, results obtained were the same.

It is concluded that this is due to the fact that the N-N bond of hydrazo benzene disufonamide is stabilized owing to the presence of sulfonamide radicals at para position.

Nitrobenzene-sulfonamide was reduced to sulfanilamide in no more than 50 % yield. It seems probable that in this reduction hydrazo-compound was not formed, because, when reaction solution was heated with small amounts of hydrochloric acid, azo-compound was not obtained.

It is generall. accepted that nitro radical will be reduced to amine in alkali media by the following course.

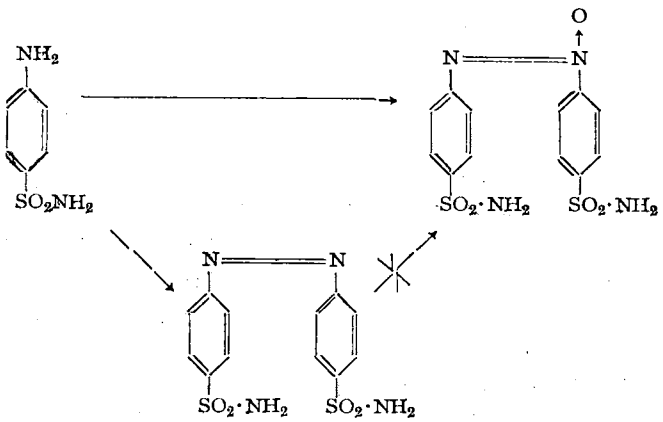
Nitro ⟶ Azoxy ⟶ Azo ⟶
Hydrazo ⟶ Amine

However in our experiment, nitrobenzene sulfonamide was reduced to amine not through hydroazo-benzene-sulfonamide, but through the other courses

that mentioned above:

Margaret K. Seikel concluded by the mixed melting point that material, which had been obtained from the oxidation of azo-compound with hydrogen-peroxide in glacial acetic acid was azo-compound. But azo compound could not be oxidized to azoxy-compound except the case of using gracial acetic acid as solvent.

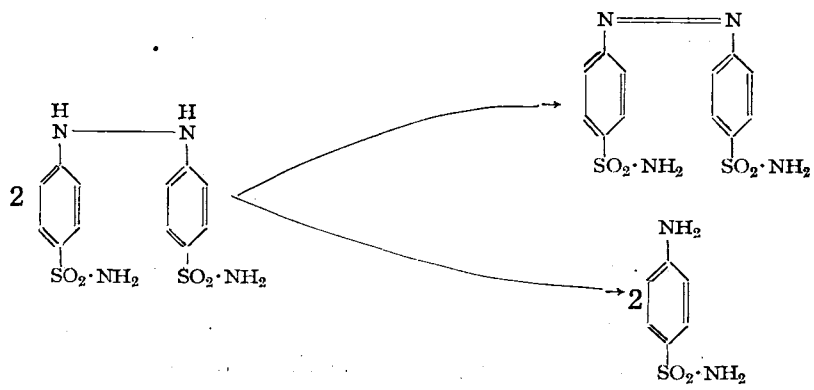
This shows that sulfanilamide is oxidized to azoxy-compound not through azo-compound. That will be very interesting fact to examine the oxidation mechanism with hydrogen peroxide.



Hydrazo-compound (D) is unstable as Margaret K. Seikel had plonted. In the recrystallization, a part was oxidized to azo-compound, even when sulfur dioxide was added. Small amounts of acids were used for catalyst of oxidation.

When hydrazo-compound was warmed by adding small amount of hydrochloric acid and sulfur dioxide to prevent oxidation, 50% of (D) were oxidized to azo-compound after 10 minutes. Although warming was continued further, the yield of azo-compound did not increase. But from the filtate which azo-compod copound was removed, sulfanilamide was produced in almost quantitative yield.

It might be concluded that self-oxidreduction occured in this case.



Anal. Calcd. for $C_{12}H_{14}N_4O_4S_2$: C. 42.1 H. 4.12 N. 16.38
Found : C. 42.02 H. 4.37 N. 16.25

TIN AND HYDROCHLORIDE : Azo-compound was reduced with tin and hydrochloride by the usual method. Complexsalt of tin was dissolved in water and filtrated. The residue was extracted with aceton containing ammoniak. The crystals obtained by removing aceton was recrystallized from acetone diluted with water. The 2.1% yield of semidin-compound (mp. 253°) was obtained.

The solution from which tin was removed by hydrogen sulfide as tinnous sulfide was allowed to stand for half a month, and 0.1g. of white needle of semidincompound, mp. 253° was produced.

Both semidin-compound did not lower each others melting points.

Anal. Calcd. for $C_{12}H_{14}O_4N_4S_2$: C. 42.1 H. 4.12 N. 16.38
Found : C. 42.35 H. 4.02 N. 16.48

From the solution from which semidin-compounds were removed 20.6% yield of sulfanilamide was produced by making alkaline with ammoniak. This did not lower the melting point with an authentic sample.

REDUCTION OF NITROBENZENESULFONAMIDE : STANNOUSCHLORIDE IN ALKALI : The mixture of 1g. of p-nitrobenzenesulfonamide, 20cc. of 10% sodium hydroxide and 2.23g. of stannouschloride was heated on the water bath. After heating 10 minutes and cooling a solution deposited red crystals of sodium salt of azocompound. The sodium salt obtained by filtration, was dissolved in water and acidified with hydrochloric-acid. The 83.7% yield of product was purified by recrystallization from 30% pyridine from which it separated crystal mp.. 313° dce.

Anal. Calcd. for $C_{12}H_{12}N_4O_4S_2$: C. 42.3 H. 3.55 N. 16.45
Found : C. 42.05 H. 3.17 N. 15.86

HYDROSULFITF : 0.95 g. Of p-nitrobenzenesulfonamide was reduced with hydrosulfite by the same preparation mentioned above. After being made basic with bicarbonate the reaction mixtures were evapolated to dryness in vacum and extracted with aceton. The residues, obtained by evaporating aceton, were recrystallized from water. 18.9-44 % yield of sulfanilamide (mp. 162—4°) was obtained, And this did not lower the melting point with authentic samples.

REDUTION OF AZOCOMPOUND OBTAINED FROM NITROCOMPOUND WITH HYDROSULFITE : This azocompound was reduced to hydrazocomponnd, mp. 223—4°

Anal. Calcd. for $C_{12}H_{14}N_4O_4S_2$: C. 42.1 H. 4.12 N. 16.38
Found : C. 41.6 H. 3.75 N. 16.46

REDUCTION OF AZOXYCOMPOUND WITH STANNOUS CHLORIDE IN ALKARI MEDIA : 1g. Of azoxy-compound was reduced to azocompound with 0.7g. of stannous-chloride in 20cc. of 10 % sodium hydroxide.

73.5% Yield of azocompound (mp. 313° recrystallized from 30% pyridine) was obtained.

Anal. Calcd. for $C_{12}H_{12}N_4O_4S_2$: C. 42.3 H. 3.55 N. 16.45
Found : C. 42.9 H. 3.8 N. 16.46

SELF-OXIDREDUCTION OF HYDRAZOCOMPOUND : A solution of 0.5g. of hydrazocompound in the mixture of 2cc. of conc. hydrochloric-acid and 5cc. of acetone containing surfurdioxide, was heated for 10 minutes on the water bath. After cooling 40.2% yiels (0.2g.) of azo-compound (mp. 311 −3°) was produced. The filtrate, removed of azo-compound, was neutralized with bicarbonate and evaporated to dryness and extracted with aceton.

The residues, obtained by evaporating aceton, was recrystalized from water. 38% Yield (0.19g.) of sulfanilamide (mp. 161−3°) was obtained.

Anal. Calcd. for $C_{12}H_{14}N_4O_4S_2$:
Found :

DIAZOATION OF SEMIDINCOMPOUND : The mixture of 0.5g. of semidin-compound and 5cc. of 10% hydrochloride were diazoated with sodium nitrite and filtrated. Recrystallization from acetone diluted with water, produced 58% yield (0.3 g.) of azimino-compound, mp. 275°.

Anal. calcd. for $C_{12}H_{11}N_3O_4S_2$: N. 19.85
Found : N. 20.3

This did not lower the melting piont with authentic samples.

PREPARATION OF SEMIDINCOMPOUND FROM HYDRAZOCOMPOUND : 10g. Of hydrazo-compound, dissolved in acetone, was poured into the 20cc. of 10% hydrochloride containing surfurdioxide and removed hydrazocompound precipitated. The filtrate was allowed to stand for 20 days and 3% yield (0.3 g.) of semidin-compound was obtained (mp. 253° recrystalized from diluted acetone).

This did not lower the melting point of semidin-compound obtained in the course of reduction.

C. 42.1 H. 3.55 N. 16.45
C. 42.6 H. 3.82 N. 16.4

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(Faculty of Pharmacy, Kanazawa University.
Pharmaceutical Research, Keiogijuku University)